#36

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: Vemuri REDDY et al

Patent No.: 4,840,896

Issued: June 20, 1989

For: HETEROPOLYMERIC PROTEIN

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Office of the Deputy Assistant Commissioner for Patent Policy and Projects

Washington, D.C.

Atty.'s Docket: REDDY=2EXT

Date: November 20, 2000

THE COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Sir:

Transmitted herewith is Application for Extension of Patent Term and Exhibits A-F (2 copies)
in the above-identified application.

[ ] Small Entity Status: Applicant(s) claim small entity status. See 37 C.F.R. §1.27.

[ ] No additional fee is required.

[XX] The fee has been calculated as shown below:

	(Col. 1) CLAIMS REMAINING AFTER AMENDMENT		(Col. 2) HIGHEST NO. PREVIOUSLY PAID FOR	(Col. 3) PRESENT EXTRA EQUALS	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
TOTAL	*	MINUS	** 20	0	x 9	$		x 18	$
INDEP.	*	MINUS	*** 3	0	x 40	$		x 80	$
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+ 135	$		+ 270	$
					ADDITIONAL FEE TOTAL	$	OR	TOTAL	$

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.

** If the "Highest Number Previously Paid for" IN THIS SPACE is less than 20, write "20" in this space.

*** If the "Highest Number Previously Paid for" IN THIS SPACE is less than 3, write "3" in this space.

The "Highest Number Previously Paid For" (total or independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment of the number of claims originally filed.

[XX] Conditional Petition for Extension of Time

If any extension of time for a response is required, applicant requests that this be considered a petition therefor.

[ ] It is hereby petitioned for an extension of time in accordance with 37 CFR 1.136(a). The appropriate fee required by 37 CFR 1.17 is calculated as shown below:

Small Entity		Other Than Small Entity	
Response Filed Within		Response Filed Within	
[ ] First	- $ 55.00	[ ] First	- $ 110.00
[ ] Second	- $ 195.00	[ ] Second	- $ 390.00
[ ] Third	- $ 445.00	[ ] Third	- $ 890.00
[ ] Fourth	- $ 695.00	[ ] Fourth	- $ 1390.00
Month After Time Period Set		Month After Time Period Set	

[ ] Less fees ($_____) already paid for ___ month(s) extension of time on _____.

[XX] Fee under 37 C.F.R. §1.20(j)(1) for receiving and acting upon application for extension: $1,120.00.

[ ] Please charge my Deposit Account No. 02-4035 in the amount of $_____.

[XX] Credit Card Payment Form, PTO-2038, is attached, authorizing payment in the amount of $1,120.00

[XX] The Commissioner is hereby authorized and requested to charge any additional fees which may be required in connection with this application or credit any overpayment to Deposit Account No. 02-4035. This authorization and request is not limited to payment of all fees associated with this communication, including any Extension of Time fee, not covered by check or specific authorization, but is also intended to include all fees for the presentation of extra claims under 37 CFR §1.16 and all patent processing fees under 37 CFR §1.17 throughout the prosecution of the case. This blanket authorization does not include patent issue fees under 37 CFR §1.18.

BROWDY AND NEIMARK
Attorneys for Applicant(s)

By: _____
Roger L. Browdy
Registration No. 25,618

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11/21/2000 00000110 2 111 $1,120.00 11/20/2000 CC

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Office of the Deputy
	)	Assistant Commissioner for
REDDY et al	)	Patent Policy and Projects
	)	
Patent No.: 4,840,896	)	Washington, D.C.
	)	
Issued: June 20, 1989	)	November 20, 2000
	)	
For: HETEROPOLYMERIC PROTEIN	)	Atty.Docket: REDDY=2EXT

APPLICATION FOR EXTENSION OF PATENT TERM

Honorable Commissioner for Patents
Washington, D.C. 20231

Sir:

In accordance with 35 USC 156, patentee, Genzyme Corporation, through the undersigned attorney, hereby applies for extension of the term of the above-identified patent. Following is the information required by 37 C.F.R. §1.740.

(a)(1) The approved product is choriogonadotropin alfa also known as recombinant human chorionic gonadotropin (r-hCG). Choriogonadotropin alfa is a water soluble glycoprotein consisting of two non-covalently linked subunits - designated α and β - consisting of 92 and 145 amino acid residues, respectively, with carbohydrate moieties linked to Asn-52 and Asn-78 (on the α subunit) and Asn-13, Asn-30, Ser-121, Ser-127, Ser-132 and Ser-138 (on the β subunit). The full amino acid

sequences of the α and β subunits of choriogonadotropin alfa are as follows:

α subunit:

```
                                    10                                  20
Ala Pro Asp Val Gln Asp Cys Pro Glu Cys Thr Leu Gln Glu Asn Pro Phe Phe Ser Gln
                                    30                                  40
Pro Gly Ala Pro Ile Leu Gln Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr Pro
                                    50                                  60
Leu Arg Ser Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser Glu Ser Thr Cys Cys
                                    70                                  80
Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met Gly Gly Phe Lys Val Glu Asn His Thr
                                    90      92
Ala Cys His Cys Ser Thr Cys Tyr Tyr His Lys Ser
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β-subunit

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                                    10                                  20
Ser Lys Glu Pro Leu Arg Pro Arg Cys Arg Pro Ile Asn Ala Thr Leu Ala Val Glu Lys
                                    30                                  40
Glu Gly Cys Pro Val Cys Ile Thr Val Asn Thr Thr Ile Cys Ala Gly Tyr Cys Pro Thr
                                    50                                  60
Met Thr Arg Val Leu Gln Gly Val Leu Pro Ala Leu Pro Gln Val Val Cys Asn Tyr Arg
                                    70                                  80
Asp Val Arg Phe Glu Ser Ile Arg Leu Pro Gly Cys Pro Arg Gly Val Asn Pro Val Val
                                    90                                  100
Ser Tyr Ala Val Ala Leu Ser Cys Gln Cys Ala Leu Cys Arg Arg Ser Thr Thr Asp Cys
                                    110                                 120
Gly Gly Pro Lys Asp His Pro Leu Thr Cys Asp Asp Pro Arg Phe Gln Asp Ser Ser Ser
                                    130                                 140
Ser Lys Ala Pro Pro Pro Ser Leu Pro Ser Pro Ser Arg Leu Pro Gly Pro Ser Asp Thr
                145
Pro Ile Leu Pro Gln
```

Asn: N-glycosylation site Ser: O-glycosylation site

(a)(2) The product was approved under Section 505(b) of the Federal Food, Drug and Cosmetic Act (21 USC 355(b)).

(a)(3) The product received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug and Cosmetic Act on September 20, 2000.

(a)(4) As the present product is a human biological product and not a drug product (as those terms are used in the Federal Food, Drug and Cosmetic Act and the Public Health Service Act), 37 C.F.R. §1.740(a)(4) is not applicable.

(a)(5) The present application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. §1.720(f). It is required that the application be filed within sixty days following the date of the FDA approval letter of September 20, 2000. The sixty day period expires on November 19, 2000. As November 19, 2000, is a Sunday, the last date on which the application could be filed is November 20, 2000 (37 C.F.R. §1.7(a)).

(a)(6) The patent for which an extension is being sought is U.S. patent 4,840,896 of which the inventors are Vermuri B. Reddy, Nancy Hsiung, Anton K. Beck, and Edward G. Bernstine. The date of issue was June 20, 1989, and the date of expiration is June 20, 2006.

(a)(7) A copy of patent 4,840,896 is attached hereto as Exhibit A, including the entire specification (including claims and drawings).

(a)(8) Attached hereto as Exhibit B is a copy of the Certificate of Correction which has issued with respect to this patent. Also attached hereto as Exhibits C and D are copies of receipts of maintenance fee payments establishing that the first and second maintenance fees were timely paid with respect to this patent.

(a)(9) The patent claims a method of manufacturing the approved product. Attached hereto as Exhibit E is a copy of a portion of Section C, "Method of Manufacture", from the original NDA submitted during the FDA approval process. Exhibit E includes pages numbered 032-049. These documents show the manufacturing process of the approved product. This manufacturing process of the approved product falls within the scope of claim 17 of the '896 patent. Also attached hereto as Exhibit F are sections 1-3.2 of a submission to the FDA dated July 26, 2000, relating to bioassay specification for the drug product. Exhibit F includes pages numbered 002-014. The following showing demonstrates the manner in which this claim reads on the method of manufacturing the approved product.

Patent Claims	Approved Product
1. A method for producing biologically active hCG comprising	See Figure CMA-5 on page 049 of Exhibit E. It shows that the final product of the purification process of the culture medium from the bioreactor is "r-hCG DRUG SUBSTANCE". Exhibit F shows the biological activity of the r-hCG

	drug product. Note the last paragraph on page 004 which shows that the mean specific activity was 26,400 IU per mg r-hCG. Thus, as the hCG can be measured in international units, biologically active hCG is produced by the method.
culturing host mammalian cells	See pages 046 and 047 of Exhibit E which indicates that the r-hCG is produced from CHO cells. See also page 034 in the section "Mode of introduction into the production strain" which indicates that the production strain is a CHO cell line. CHO is Chinese hamster ovary cells. Hamster cells are mammalian cells.
comprising a first expression vector encoding the α subunit of said hCG and	The section at the bottom of page 034 of Exhibit E, entitled "Mode of introduction into the production strain", states that cells were co-transfected with uncut pHαDHFR containing the α hCG and pHLHβODC containing the β-hCG gene. The construction of the α hCG gene expression vector is discussed at pages 032 and 033. Accordingly, it is clear that the α and β subunits are introduced in separate vectors. Thus, the mammalian cells comprise a first expression vector encoding the α subunit of hCG.
a second expression vector encoding the β subunit of said hCG.	The construction of the β hCG gene expression vector is discussed on pages 033 and 034 of Exhibit E. As discussed above, the paragraph at the bottom of page 34 indicates that the α and β gene vectors are introduced separately. Thus, the mammalian cells also

comprise a second expression vector encoding the β subunit of hCG.

(a)(10)(i) The effective date of the Investigational New Drug (IND) application was October 2, 1995, and was assigned IND number 48934. The New Drug Application was initially submitted on November 23, 1999, and was assigned NDA number 21-149. The NDA was approved on September 20, 2000.

(a)(11) The following is a brief description of significant activities undertaken by the marketing applicant during the applicable review period:

IND submitted	September 29, 1995
IND received by FDA	October 2, 1995
FDA Action Letter and Acknowledgement of Receipt	October 10, 1994
Study 7927 submitted to IND	November 28, 1995
Approval for 7927 to commence	February 1, 1996
7927 Completion Date	April 1998
NDA submitted	November 23, 1999
NDA received	November 24, 1999
FDA letter acknowledging receipt	November 30, 1999
USAN name adopted	February 23, 2000
Correction to USAN information	March 22, 2000
Submission of 120-day safety report and additional clinical and bioequivalents reports	April 7, 2000

Submission of information package CMC for diluent	June 16, 2000
Submission of additional financial disclosure information	June 28, 2000; July 5, 2000
Bioassay specification for the drug substance and the drug product	July 26, 2000
Withdrawal of 500 mcg and 250 mcg doses	August 1, 2000
Withdrawal of alternate diluent manufactured by Pharma Hameln	August 3, 2000
Response to CMC request for information	August 7, 2000
Addition of microplasma testing for drug substance release	August 29, 2000
Withdrawal of alternate packaging facility	September 6, 2000
NDA approval	September 20, 2000.

(a)(12) Applicant is of the opinion that patent 4,840,896 is eligible for patent term extension. Applicant claims a length of extension of 1054 days which will extend the patent through May 9, 2009. The length of extension was determined as follows using the following dates and time periods as set forth in 37 C.F.R. §1.775:

(c)(1)	10/10/1995 through 11/24/1999	=	1506
(c)(2)	11/24/1999 through 09/20/2000	=	301
(c)	(c)(1)+(c)(2)	=	1807

(d)(1)(i)	none	=	0
(d)(1)(ii)	not known	=	0
(d)(1)(iii)	((c)(1)-(d)(1)(i))+2	=	753
(d)(1)	(c)-(d((1)(i)-(d)(1)(ii)-(d)(1)(iii)	=	1054
(d)(2)	06/20/2006 + (d)(1)	=	05/09/2009
(d)(3)	09/20/2000 + 14 years	=	09/20/2014
(d)(4)	earliest of (d)(2) and (d)(3)	=	05/09/2009
(d)(5)(i)	06/20/2006 + 5 years	=	06/20/2011
(d)(5)(ii)	earliest of (d)(4) and (d)(5)(i)	=	05/09/2009
(d)	(d)(5)(ii)	=	05/09/2009

(a)(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(a)(14) Attached hereto is PTO Form 2038, Credit Card Payment Form, authorizing payment in the amount of $1,120.00 in accordance with 37 C.F.R. §1.20(j)(1) for receiving and acting upon the application for extension.

(a)(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the present application are to be directed is as follows:

Roger L. Browdy
BROWDY AND NEIMARK, P.L.L.C.
624 Ninth Street, N.W.
Suite 300
Washington, D.C. 20001-5303

Telephone: 202-628-5197
Facsimile: 202-737-3528.

(a)(16) The undersigned certifies that attached hereto is a duplicate of all of the present application papers.

(a)(17) I, the undersigned Roger L. Browdy, hereby declare and state that I am a patent attorney authorized to practice before the Patent and Trademark Office and have general authority from Genzyme Corporation, the owner of patent 4,840,896 to act on their behalf in patent matters relating to patent 4,840,896. I have reviewed and understand the contents of the foregoing application being submitted pursuant to 37 C.F.R. §1.740. I believe that the patent is subject to extension pursuant to §1.710. I believe that an extension of the length claimed, subject to any reduction caused by a determination by the Secretary of Health and Human Services under 35 USC 156(d)(2)(B) that applicant did not act with due diligence, is justified under 35 USC 156 and the applicable regulations. I believe that the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.720.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Patent Owner

By _____
ROGER L. BROWDY
Registration No. 25,618

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